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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,764	10/24/2003	Stuart B. Levy	16534-539001US	8952

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EXAMINER	
EPPS -SMITH, JANET L	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
12/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,764	LEVY ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Smith	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,37-47,54,57,59,60 and 62-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,37-47,54,57,59,60 and 62-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09-08-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The objection to the claims as improper under 37 CFR 1.57(c) is withdrawn in response to Applicant's amendment to the specification filed 09/08/09, and Applicant's statement that the amendment did not include any new matter.

2. The amendments filed on 09/08/2009 are acknowledged. Thus currently, claims 1, 37-47, 54, 57, 59-60, and 62-65 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claim Rejections - 35 USC § 112

4. Claims 1, 37-47, 54, 57, 59-60, and 62-65 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons of record and those set forth below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

5. The instant claims are drawn to a method for treating a Disease Treatable by Modulation of RNA (DTMR) associated with splicing of nuclear RNA, comprising: administering to said subject an effective amount of a tetracycline compound of formula (I) to modulate splicing, wherein said DTMR associated with splicing of nuclear RNA is spinal muscular atrophy.

6. Applicant's arguments filed 09/08/2009 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the examiner has simply misinterpreted the findings set forth in the references used to support her position.

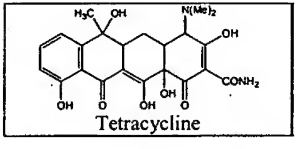
7. First, Applicants argued that the statement quoted by the examiner from the Liu et al. reference does not teach unpredictability. Contrary to Applicant's assertions, the Liu et al. reference clearly demonstrates that although the chemically modified tetracyclines all share a core structure they display varied chemical properties depending upon the relative lipophilicity of the compound. It is clear that changing the chemical class of the various substituents within the ring structure of the tetracycline core has the potential to alter the lipophilic properties of the compound, and therefore have the potential to alter the pharmacokinetic properties of the compound as well. This aspect of Liu et al. is a classic example of the known unpredictability associated with the chemical arts; see MPEP 2164.03[R-2]. The instant claims are drawn to an exponential number of potential compounds all sharing a common core structure. The teachings of Lui et al. are directly relevant in the instant case, since there are numerous positions within the core structure that may include modifications. The potential for the various modified tetracycline compounds of formula (I) to possess varied chemical properties is tremendous. Applicants have not provided a direct correlation between the behavior of a single species of tetracycline compound of formula (I) and the production of a therapeutic benefit in a patient, particularly in regards to the amelioration of spinal muscular atrophy. Moreover, even if such a correlation existed, the teachings of Lui et

al. would suggest that the pharmaceutical benefit of a single species of formula (I) would not necessarily be predictive of a therapeutic benefit associated with the administration of compounds of the entire genus of formula (I).

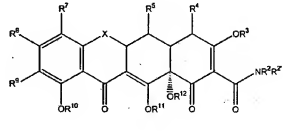
8. Secondly, Applicants argued that the testing and screening of Hertweck et al. amounts to routine experimentation, as the art typically engages in such experimentation. However, Applicants did not address how the experimentation in Hertweck et al. would teach the skilled artisan how to determine which tetracycline derivative is appropriate for treating spinal muscular atrophy. Applicants have simply dismissed the questions raised by the examiner as being routine experimentation.

9. Thirdly, in regards to Chakkalakal et al., Applicants argue that these findings are not applicable. However, contrary to Applicant's assertions, although the results shown in Chakkalakal et al. are related to gentamicin, the results demonstrate the inability of *in vitro* based cellular assays to make absolute predictions about *in vivo* therapeutic efficacy. Applicant's have provided a single example of the treatment of two independent murine macrophage cells lines (J774.2 and RAW 264.7) in which there is up-regulation or down regulation of mRNA as assed by microarray technology (see example 3). There is no disclosure if these murine macrophage cells are an art accepted model for SMA. Example 4 investigates the *in vitro* cytotoxicity of two tetracycline compound derivatives (minocycline and doxycycline) on Cos-1 and CHO-K1 cells and Example 5 investigates the *in vitro* anti-bacterial activity of 2 undisclosed tetracycline derivative compounds.

10. In regards to Andreassi et al., Applicants argue neither aclarubicin nor doxorubicin is similar in structure to the claimed compounds of formula (I). Therefore, Applicants concluded that any unpredictability described in Andreassi is not pertinent to the currently claimed methods which comprise the administration of a compound of formula (I). Contrary to Applicant's assertions, although Applicants have amended the claims to recite wherein the tetracycline compound of formula (I) is not tetracycline, it is clear that the disclosed invention and the claims as originally filed encompassed tetracycline within the scope of the method. Therefore, although Applicants wish to dismiss the teachings of Andreassi et al. away as being inapplicable, the reference clearly teaches that tetracycline which is a species of the disclosed invention and the originally claimed invention, showed no activity in altering gene splicing of SMN2 mRNA in cells derived from type I SMA patients. Tetracycline, as reproduced from page 12 of the specification as filed, is a species of formula (I) of the instantly claimed invention.



Tetracycline



(I). If the prior art teaches that tetracycline, a species of formula (I) is not effective in to alter incorporation of exon 7 into *SMN2* transcripts, there is no reason to believe that other compounds highly similar to tetracycline would be able to alter splicing of *SMN2* transcripts, or further would have the ability to ameliorate SMA in a patient. Thus, contrary to Applicant's assertions, the teachings of Andreassi et al. are directly relevant

to the claimed invention. Applicant's dismissal of the teachings of this reference is improper. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics,* 8 USPQ2d 1217 (Fed. Cir. 1988)). In the instant case, the prior art directly suggests that the claimed method would not work as Applicant's suggest. However, Applicants have not provided any evidence that the teachings of Andreassi et al. are inaccurate. Applicants have simply attempted to amend around the teachings of this reference by excluding tetracycline. However, as stated above, the specification and original claims clearly included tetracycline within the scope of the claimed method of treating a DMTR.

Further, Applicants argued that Applicants are not required by the enablement requirement to provide a working example, much less an example of *in vivo* treatment of a DTMR associated with splicing. Applicants further cited that compliance with the enablement requirement does not turn on whether an example is disclosed, and that "The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)." Although the examiner agrees with Applicant's wherein the claimed invention is otherwise predictable, in the present case, the prior art provides strong evidence that would suggest that tetracycline based compounds do not function to alter the splicing of *SMN2* transcripts, or further to treat SMA. As per MPEP § 2164.02

"When considering the factors relating to a determination of non-enablement, if all the other factors point toward enablement, then the absence of working examples will not by itself render the invention non-enabled." In the instant case there are multiple factors which point away from enablement, the fact that Applicants completely lack a working example, further supports a finding of non-enablement.

Additionally, Applicants argued that the specification provides additional guidance for evaluating the therapeutic effects of compounds of formula (I) in treating SMA. However, Applicants admit that the teachings of the specification are "generic" in nature and thus not specific for treating SMA. The examiner maintains that the skilled artisan would be forced to perform undue experimentation in order to make and use the claimed invention. Applicant's arguments that the specification provides assays for measuring RNA splicing are irrelevant, as the specification does not disclose how splicing is supposed to be modulated for the treatment of SMA. Thus the skilled artisan would not be able to recognize if a change of splicing was a "treatment" as there is no disclosure of successful splicing modulation, or any teaching of what it ought to be in different disease states.

As stated in the prior Office Action, the invention involves a method of treating Spinal Muscular Atrophy (SMA) comprising the administration of *any* species of tetracycline derivative compound that falls within the scope of formula (I) as recited in the instant claims, wherein the compound is administered in an "effective amount" to modulate (i.e. increase, decreases, or etc.) the nuclear RNA splicing of an undefined gene target that is associated with Spinal Muscular Atrophy in any subject. The scope

of the claimed method involves the modulation of subject's nuclear RNA splicing of an undefined mRNA target in the subject, including activation of cryptic splice sites, silencing of splice sites, silencing of exonic or intronic splicing enhancers, silencing of exonic or intronic splicing silencers, the alteration of the binding component of the splicing machinery to the RNA, or affecting the intermolecular interactions between components of the splicing machinery. Furthermore, the method reads on treating humans.

Applicants have not taught one of skill in the art how to decipher which of the thousands of tetracycline derivatives in the instant specification would be able to overcome known obstacles in the art (e.g. as taught by Andreassi et al.). Applicant's have not shown any in vivo data to investigate the cellular uptake, half-life, clearance, etc. of the thousands of compounds disclosed, not how to address these issues, other than altering the effective amount based on compound, and size and weight of the subject. A skilled artisan would therefore be required to determine how each of the thousands of tetracycline compounds reacts *in vivo* in order to determine which one to even begin testing for treating a patient with SMA.

Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, including the highly unpredictable art, the scarcity of working examples provided by applicant, the lack of guidance by the applicant, and the broad nature of the invention it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

11. The rejection of claims 1, 37-47, 54, 57, 59-60, and 62-65 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in response to Applicant's amendment to the specification.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

13. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633